ISIS 301012 Does Not Interact With Currently Marketed Lipid Lowering Drugs

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Data From Drug-Drug Interaction Study Continues to Support Potential of Drug to Lower Cholesterol

CARLSBAD, Calif., March 13, 2006 /PRNewswire-FirstCall via COMTEX News Network/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) today announced additional data from clinical studies of ISIS 301012 that continue to broaden the potential profile for the drug to treat patients with cardiovascular disease. In a drug-drug interaction study, ISIS 301012 did not interact with simvastatin or ezetimibe, currently available lipid lowering drugs with which ISIS 301012 may be dosed in combination. In this study and consistent with the growing body of data on ISIS 301012, the drug also reduced cholesterol, LDL-C, and was well tolerated. ISIS 301012, a second-generation antisense drug, inhibits apop-100, a protein critical to the synthesis and transport of the "bad" cholesterol involved in heart disease -- low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein (VLDL).
Lowering cholesterol and triglyceride levels is a key component to the prevention and management of cardiovascular disease.

In this study, healthy volunteers were treated with 200 mg of ISIS 301012 on four days over approximately a two-week period. On the final day of dosing, the healthy volunteers were treated with 40 mg of simvastatin or 10 mg of ezetimibe. The pharmacokinetic profiles of simvastatin, ezetimibe, and ISIS 301012 alone were then compared to the profiles in the presence of ISIS 301012 combined with simvastatin or ezetimibe on the final day of dosing. There were no clinically significant effects of simvastatin or ezetimibe on the pharmacokinetics of ISIS 301012. Nor did ISIS 301012 affect the pharmacokinetics of simvastatin or ezetimibe.

In this study, after only four doses, ISIS 301012 achieved a median reduction of 33% in apoB-100 and median reduction of 28% in LDL-C, and there were no adverse events. As previously reported, healthy volunteers with elevated cholesterol, who were treated with an average of 350 mg/week of ISIS 301012 for one month, achieved a median reduction of 60% in apoB-100, 54% in LDL-C and 46% in serum triglycerides. Data from the two studies demonstrate, when combined with earlier data, the exceptional consistency of effect of ISIS 301012.

"Because patients with cardiovascular disease are often treated with many drugs, demonstrating that ISIS 301012 does not interact with two major drugs used in such treatment, simvastatin and ezetimibe, is an important enhancement of the profile of ISIS 301012 and supports the use of ISIS 301012 in combination with statins or ezetimibe in treating patients with high cholesterol," said Mark Wedel, MD, JD, Senior Vice President of Development and Chief Medical Officer at Isis Pharmaceuticals. "In addition to broad activity of ISIS 301012 in reducing all of the bad lipids plus triglycerides, these data also support the use of ISIS 301012 in patients on currently available therapies who are still not reaching their targeted cholesterol levels. If ISIS 301012 continues to show strong activity when combined with cholesterol lowering drugs that are currently being marketed, ISIS 301012 could greatly improve the health and well-being of numerous patients who are suffering from high cholesterol and cardiovascular disease."

"In addition, it is important to note that some current drugs have the ability to reduce LDL-C but have only a modest effect on triglyceride levels, while other drugs are more effective at lowering triglyceride levels but are less effective in lowering LDL-C," Dr. Wedel added. "With the ability to reduce both LDL-C and triglyceride levels, and having confirmed that ISIS 301012 does not interact with simvastatin and ezetimibe, the potential treatment of ISIS 301012 when combined with currently available therapies could help many patients."

In September 2005, Isis initiated the Phase 2 development program of ISIS 301012. Phase 2 trials of ISIS 301012 are being conducted in patients with high cholesterol. Isis is conducting a Phase 2 single-agent trial designed to optimize dose and frequency of dosing, and to further evaluate the safety and efficacy of ISIS 301012 in patients with high cholesterol. Isis is also conducting a Phase 2 trial of ISIS 301012 in combination with statin therapy in patients with high cholesterol. Isis is also conducting Phase 2 studies of ISIS 301012 in patients with familial hypercholesterolemia (FH), a genetic disorder that causes extremely high cholesterol levels and results in the early onset of heart disease.

ABOUT CHOLESTEROL AND CARDIOVASCULAR DISEASE

According to the American Heart Association, an estimated 106.9 million American adults have total blood cholesterol values of 200 mg/dL and higher, and of these about 37.7 million American adults have levels of 240 or above. In adults, total cholesterol levels of 240 mg/dL or higher are considered "high risk". Levels from 200 to 239 mg/dL are considered "borderline-high risk". Low-density lipoprotein, or LDL, known as the "bad" cholesterol, can clog arteries, increasing the risk of heart attack and stroke.

According to the World Health Organization (WHO), heart disease and stroke kill 17 million people a year, which is almost one-third of all deaths globally. By 2020, the WHO projects that heart disease and stroke will become the leading cause of both death and disability worldwide, with the number of fatalities projected to increase to over 20 million a year and by 2030 to over 24 million a year.

Familial hypercholesterolemia is a dominantly inherited genetic condition that results in markedly elevated LDL (low-density lipoprotein) cholesterol levels beginning at birth, and resulting in heart attacks at an early age. Affected people have consistently high levels of low-density lipoprotein, which leads to premature atherosclerosis of the coronary arteries.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 12 antisense drugs in development to treat cardiovascular, metabolic, inflammatory and ocular diseases, and cancer. In its Isis division, Isis is developing and commercializing the TIGER biosensor system, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding the development, therapeutic potential and safety of ISIS 301012 to lower high
cholesterol. Any statement describing Isis’ goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis’ goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing, and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Isis’ forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis’ forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2004, and its quarterly report on Form 10-Q for the quarter ended September 30, 2005, which are on file with the SEC. Copies of these and other documents are available from the Company.

SOURCE Isis Pharmaceuticals, Inc.

Navjot Rai, Corporate Communications of Isis Pharmaceuticals, Inc., +1-760-603-2331